Summit on Development of Infectious Disease Therapeutics

September 26-27, 2000
Bethesda, Maryland

Summary Draft Report of the Antibacterial Working Group

Chairpersons:
Dr. Marissa A. Miller
Dr. Gail H. Cassell

The Antibacterial Working Group had a rich representation from various sectors including large and small pharmaceutical companies, biotechnology firms, academia, and government. The working group described current resources available for drug development, incentives or enhancements that would further development efforts, and the potential for new collaborations between the public and private sectors for development of drugs to address public health needs. The working groups' exchanges, and this summary, attempt to address the five discussion questions outlined at the beginning of the meeting.

Background and Existing Resources:

The working group identified two critical reasons for development of new antibacterial drugs: the development of resistance to common antibiotics which limits the usefulness of current therapeutics, particularly among nosocomial pathogens; and the lack of drugs to treat chronic and complex bacterial diseases such as tuberculosis (TB), which are more prevalent in the developing world, and thus do not offer high financial return. Antimicrobial resistance is growing and spreading in industrialized and developing countries alike, and is reducing therapeutic options particularly in hospital settings and in the face of serious, chronic bacterial diseases. The emergence of intermediate susceptibility to vancomycin in Staphylococcus aureus and vancomycin resistance in Enterococcus faecium, have resulted in treatment failures and increasing healthcare costs. Worldwide, tuberculosis causes nearly 3 million deaths per year and is the leading infectious killer of youths and adults. Control of this disease is hampered by the lack of an effective vaccine to prevent pulmonary tuberculosis in adults. Furthermore, treatment regimens involve multiple drugs administered over prolonged periods. The cost and difficulty in administering these drug regimens limits treatment availability in large areas of the developing world, with the WHO estimating that only 21% of TB patients worldwide are receiving adequate regimens. A consequence of partial treatment in large numbers of patients is the development and spread of multi-drug resistant strains, resulting in a global crisis. New or improved therapeutic agents are urgently needed.

Research and development leading to the licensing of new antibacterial agents is influenced and limited by the need of industry to meet financial goals. Competition exists within a company for investment dollars. A clear financial benefit is necessary to justify development of a new drug. With the appropriate support or incentive, the balance can be tipped in favor of developing a drug to address public health need. For small companies, timely support is essential to enable financial commitments to a new drug development endeavor.

The pharmaceutical representatives acknowledged that market data are largely unavailable, yet essential to make a convincing argument to pursue the development of drugs for public health needs. Specifically what is needed is information on the incidence and prevalence of infections, global market analyses, economic burden of disease, drug development costs, and impact of resistance. For example, the emerging markets in China, Russia, and South America need to be recognized and described. Over the next 10 years, augmented public health infrastructures will also be necessary in these locations. International cooperative training programs are needed to

support drug development and drug testing in developing countries. The government, in particular the Centers for Disease Control and Prevention, could have a role in obtaining and making marketing information available. Industry might be interested in paying an annual fee in order to have a reliable data source. NIAID could have a role in establishing and supporting scientific research infrastructures.

New Opportunities for Drug Development for Bacterial Diseases

Whereas the group acknowledged factors limiting development of new products, they also suggested that incentives and provision of new and additional resources should be explored to promote drug development for public health priorities. Using NIH resources to support research from the concept to proof of principle; for example, by supporting screening and assay development, could serve to move a lead compound or target down the developmental pathway. Collaborative research between academia and industry is occurring and could be further encouraged by NIAID acting as a liaison between companies and academic institutions. Collaboration between academic and private partners could be applied to the area of translational/functional genomics, which has been identified as a scientific gap area. One mechanism to achieve this might be by funding combination efforts on functional genomics research, e.g., program projects or cooperative agreements that mandate links of basic research with industry.

Companies may have corporate philosophies/approaches that make them more or less receptive to interactions with the government either by agreement or by grant mechanisms. NIH grants may have the greatest impact on smaller companies, which typically need considerable support for licensing and drug development; NIH can also provide other kinds of resources that individual investigators need, e.g., toxicology, and animal testing. Challenge grants soliciting specific research seem to be a way to build momentum for development of specific drugs within companies. This approach was successful in the Tuberculosis drug arena because it allowed companies to leverage their resources with government funding. Timeliness is extremely important, especially for smaller companies. Thus, grant mechanisms that make more rapid awards are important. Grants should also be shaped to foster interdisciplinary approaches.

Moving Forward

The working group discussed at length the impediments to new antibacterial drug development and how these might be overcome. There are two main ways in which development of new drugs might be enhanced: "push" mechanisms that reduce the cost of producing the drugs, and "pull" mechanisms that increase the market for them. The working group considered many types of incentives including actions during both pre and post development phases.

Incentives

The major cost in drug development is not discovery of compounds, but rather development and licensure, particularly the expense of clinical trials. Incentives are needed especially for orphan drug development. Patent extension is a possible solution, but consideration must be given to providing patent extension for profitable products other than the antibacterial product developed for a niche market. Incentives should be explored for out licensing of compounds from large pharmaceutical companies to others with smaller requirements for return on investment. Coupled with this should be extending remaining patent lives, as short patent lives can negatively impact upon decisions to license in new compounds. Limitations to this approach include the necessity for legislative action by Congress. Another possible solution, the establishment of a purchase fund to guarantee sales, may not be attractive to industry because of the uncertainty about long-term government commitment. A third possible incentive, tax breaks, may be too cumbersome for companies to make them worthwhile. The issue of incentives is one that the FDA representatives indicated they would study and consider.

Logistical/Administrative/Legal Impediments
A significant impediment to the development of new antibacterial products is the difficult balance between attainment of market share and judicious use of these new and novel products. The emergence and spread of antimicrobial resistance has necessitated discussions between industry and government that new products be used for limited indications and in some cases carry restricted labeling. These issues influence the marketing and potential profits derived from these products and are disincentives to the development of new products.

A major impediment to government supported drug development is the perceived bias against these applications in the NIH review process. Drug development applications are not considered basic research and hence do not score well compared to hypothesis driven proposals. Proposals submitted by large and small pharma frequently are not well received or appreciated by academic-based study sections. The working group suggested a possible solution would be the creation of a new drug development study section in the model of the vaccine study section.

Industry voiced a concern about the protection of intellectual property in potential government interactions. In order to be successful, government interactions must assure protection of intellectual property including "composition of matter" as well as "new use" rights.

Support of Basic Research
All participants viewed NIH's contribution to basic research as the government's most significant and important contribution to drug development. Gaps of understanding remain in the areas of microbiology, microbial physiology, and antimicrobial resistance mechanisms. In addition, the unfavorable review environment has eroded the confidence that antimicrobial resistance grants have a reasonable chance of being funded. What is needed is a clear commitment by NIAID to these research areas, including studies examining how dosing can reduce the emergence and spread of resistance. Another area of basic research that could significantly benefit drug R&D is development of technologies leading to expansion of known chemical entities.

Training Needs
The working group supported the creation of additional training and fellowship opportunities through government and industry for the next generation of researchers. There is a need for NIAID to support young investigators in microbiology. During the past 20 years, there has been an emphasis on molecular biology, resulting in fewer students in microbiology. Many undergraduate programs do not even offer microbiology courses. There is also a need for mentors who define themselves as microbiologists, and for training fellows in microbial physiology. NIH should also sponsor research and support training in functional genomics of pathogens as a way to capture student interest in microbiology and infectious disease research.

Scientific/Technical Hurdles
Several bottlenecks were identified where resources in both the public and private sector were deemed to be inadequate to advance promising products. The first of these involves medicinal and combinatorial chemistry studies. The medicinal chemistry stage is a key decision point for both large and small pharma, with respect to whether a product moves forward. NIH may want to target this stage for resource support, particularly for small companies. NCI and DAIDS have this capability; however, the program in DAIDS does not have the capacity to handle additional volume.

Another bottleneck involves the screening of compounds, which has two aspects: the libraries themselves and the screening assays. NIH could consider developing/administering/or setting up a foundation for a centralized library of compounds for screening. Selection of compounds for screening has remained limited to traditionally chosen compounds. There is a need for new methodologies and secondary screens to expand the pool of compounds, and hence, expand the

current limited chemical environment. The NCI chemical library has been used extensively by DAIDS; it's a potential resource to which there is already access. There is now an effort to develop a WEB-Site devoted to AIDS and antimicrobials. It may also be possible to form screening contracts to gain access to libraries of private companies.

Another critical area is clinical trials, particularly those that are complex and difficult to implement such as for tuberculosis drugs. A spectrum of NIH support can be formulated for clinical trials, from design of the trials to actual conduct of trials. There's a need for large groups of accessible patients with bacterial infections. Currently, NIAID supports the Tuberculosis Research Unit, which provides infrastructure for Phase I-II trials, but is now being extended to Phase III trials. Publishing successful clinical trial data is standard industry practice; however, there is reluctance to publish data from failed trials. This information is potentially very valuable and companies should be encouraged to make it, as well as their clinical trials protocols accessible. It would be optimal if all of this information could be archived in an accessible database.

In the antibacterial area, the working group suggests NIAID/NIH foster a network of investigators who understand not only the infectious diseases, but also trial design, and provide them with a level of salary support to compensate for the large amount of time and effort involved in managing clinical trials. The creation of the new Bacteriology and Mycology Study Group is a first step in this direction. Adequate support for this endeavor is important to assure cutting edge trials can be accomplished in difficult or hard to reach populations.

The lack of diagnostic tools for many drug resistant bacteria further complicates the decision to develop a new product when the market or population for use cannot be readily defined. The development of point of care diagnostics would create both an increased market for new antibiotics and a tool with which physicians can prescribe narrow spectrum antibiotics. The working group supported government involvement in the development of new diagnostic methodology for detection and identification of drug resistant bacterial pathogens.

Working Together

The working group reviewed a number of successful and unsuccessful models of government and industry collaboration. The successful models are the Small Business Innovative Research and Small Business Technology Transfer Programs (SBIR, STTR) and the Challenge Grant Program. Although there is significant effort involved in preparing a grant application, once small companies get into SBIR/STTR programs, they view them as an asset. These programs have proved very helpful in enabling small companies to leverage their resources. To be most effective, SBIR and STTR awards should be made faster, more efficient, and with higher budgets. One problem with STTRs, as currently formulated, is the budget division between academia and industry--with neither party getting sufficient funding for rapid progress. Challenge grants soliciting specific research are a way to build momentum for development of specific drugs within companies. The Challenge Grant Program was timely and of benefit because it required company commitment to resources. Being milestone driven, it was compatible with industrial approaches to drug development. Industry suggested continuation of the Challenge Grant Program. Of less positive impact was the Cooperative Research and Development Agreements, which are perceived as too slow to be of value to industry in many situations. When a product is further along in development, companies tend to steer away from CRADAs and from government partnerships in general. The working group felt the Defense Advanced Research Projects Agency (DARPA) approach and new public/private/government partnerships should be studied and considered for the future.

With any type of support, timeliness is extremely important. It is especially important for smaller companies that frequently do not have the resources to tolerate delays. New models and new mechanisms are needed for more rapid support of innovative development research in industry. One possible model could involve P01's or cooperative agreements requiring industry, academic

and government partnerships such as the National Cooperative Drug Development Group (NCDDG) programs or the Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP).

Summary and Key Issues:

There are a number of key roles NIAID can and should play in the development of drugs for diseases of public health impact, these include:

- supporting basic research, with increased focus in the areas of microbiology, microbial physiology, and antimicrobial resistance
- targeting of medicinal chemistry, as a critical area necessary to facilitate antibacterial drug development
- expanding the scope of clinical trial support, including making available appropriate expertise in study design and increased capability and capacity to conduct Phase III clinical trials
- continuing and expanding the Challenge Grant Program, maintaining the requirement for industry matching of dollars and expedited review
- facilitating the interaction of academia and industry in the area of functional genomics and preclinical and clinical drug development through such mechanisms as program project or cooperative agreements
- investing in the development of new diagnostic methods to augment prudent use activities and likely stimulate the commitment of industry to new drug development, and
- creating a Drug Development Study Section, analogous to the Vaccine Study Section.